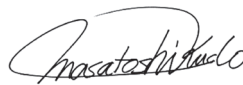


**Editorial**

# Breakthrough Imaging in Hepatocellular Carcinoma

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The ultrasound (US) contrast agent, SonoVue<sup>®</sup>, has been approved for use worldwide. Conversely, Sonazoid<sup>®</sup>, which was approved in Japan ahead of other countries in January 2007, is also currently used in Korea, China, and Norway, although its use is gradually spreading to other countries. Sonazoid<sup>®</sup>-enhanced US is considered a breakthrough imaging technology because it has drastically changed clinical practice, especially in the treatment of hepatocellular carcinoma (HCC) [1, 2].

Sonazoid<sup>®</sup>-enhanced US imaging is divided into two phases, namely the vascular and Kupffer phases, based on the *in vivo* dynamics of the agent. Sonazoid<sup>®</sup>-enhanced US is extremely sensitive for the detection of intranodular blood flow in hepatic tumors, and it is superior to the sensitivity of triphasic multidetector-row computerized tomography (MDCT) [3]. In other words, contrast-enhanced US (CEUS) detects arterial blood flow in real time, resulting in 100% sensitivity. This means that the detection sensitivity of CEUS for intranodular arterial blood flow is higher than that of MDCT. It is also well known that CT hepatic angiography (CTHA), in which CT and angiography are performed concurrently, is inferior to CEUS in terms of the detection sensitivity for intranodular arterial blood flow. SonoVue<sup>®</sup>-enhanced US is normally performed to display intranodular blood flow for a thorough examination of previously detected nodules by B-mode US. However, unlike SonoVue<sup>®</sup>, the Kupffer phase of Sonazoid<sup>®</sup>-enhanced US is used to survey the entire liver by depicting Kupffer defects. Intranodular vascularity is subsequently detected by re-injecting Sonazoid<sup>®</sup> (defect reperfusion imaging) [2, 4], thus enabling the concurrent detection and definitive diagnosis of HCCs. Accordingly, Sonazoid<sup>®</sup>-enhanced US can be used for visualizing B-mode ill-defined nodules as well as for surveillance and staging, which is not feasible with CEUS using SonoVue<sup>®</sup>.

The Kupffer phase of Sonazoid<sup>®</sup>-enhanced US is an extremely important phase for the following reasons:

- (1) All hypervascular HCCs are well-to-moderately differentiated HCCs, and thus show decreased or absent Sonazoid<sup>®</sup> uptake in the Kupffer phase.
- (2) Among precancerous lesions such as dysplastic nodules (DNs) and early HCCs [5], those with a poor arterial blood supply, but with a preserved portal venous supply, appear isoecho-

ic relative to surrounding tissues in terms of Sonazoid<sup>®</sup> uptake in the Kupffer phase.

(3) The differentiation between a DN and a well-differentiated early HCC is difficult because neither show defects in the Kupffer phase. However, hypovascular nodules that are hypoechoic in the Kupffer phase may be diagnosed as early HCCs [6].

In the future, it will be desirable to consider these findings in combination with gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DPTA)-enhanced magnetic resonance imaging (Gd-EOB-MRI).

Sonazoid<sup>®</sup>-enhanced US is also useful for the differentiation of various liver tumors. Tumors can be differentiated easily if they display different contrast enhancement patterns [7]. When the US shows characteristic vascular architecture and hemodynamics, it is normally unnecessary to perform CT or MRI to obtain additional information in order to make a definitive diagnosis [4, 7].

In recent years, by applying highly stable Kupffer-phase imaging and real-time vascular imaging in Sonazoid<sup>®</sup>-enhanced US, a novel and extremely useful US technique called defect reperfusion imaging has been developed [2, 8]. This can accurately localize B-mode ill-defined nodules in typical HCCs that are hypervascular, and that washout in the late venous phase on MDCT [1, 2]. With this technology, B-mode ill-defined nodules are detected first as defects in the stable Kupffer phase, and then Sonazoid<sup>®</sup> is re-injected to examine whether arterial blood flow is present within the Kupffer defects. This breakthrough diagnostic imaging technique was developed by simply reversing the conventional way of thinking and it requires no special equipment or analysis. In other words, nodules with typical CT findings of early enhancement with late washout are displayed as defects in the Kupffer phase, and then arterial vascularity in the defects are visualized using Sonazoid<sup>®</sup> re-injection. By incorporating these ideas, nodules that display typical findings on CT images, but that are ill-defined on B-mode US are identified with almost 100% sensitivity. In defect reperfusion imaging, nodules that are not enhanced after the re-injection of Sonazoid<sup>®</sup> may be identified as nodules that are different from those detected on dynamic CT imaging. Accordingly, this imaging can be used as an innovative technique to assist in the treatment of HCC [9–12]. Furthermore, defect reperfusion imaging is useful in various applications, such as screening for HCC in cases of liver cirrhosis with a coarse parenchyma [13], the identification of local recurrence after treatment, contrast US-guided needle insertion, the evaluation of treatment response following radiofrequency ablation (RFA) [14], or transarterial chemoembolization (TACE) [15–17].

Various imaging modalities including CT, MRI, and B-mode US are widely available in current clinical practice. Therefore, it is important to know when to apply Sonazoid<sup>®</sup>-enhanced US, as summarized below.

(1) When a screening US shows a nodular lesion with findings indicative of a hemangioma: CEUS enables the definitive diagnosis of a cavernous hemangioma in the outpatient setting, making dynamic CT imaging and MRI unnecessary.

(2) When a liver mass displays the ‘spoke-wheel’ sign by color Doppler, and the patient is negative for viral hepatitis, tumor markers, clinical signs of liver disease, and in the absence of a known primary neoplasm:

A definitive diagnosis of focal nodular hyperplasia (FNH) is possible if CEUS shows the ‘spoke-wheel’ sign and has iso- or high-uptake in the Kupffer phase. Therefore, angiography only to make a diagnosis of FNH has proved to be unnecessary in recent years. With respect to the ability to visualize the ‘spoke-wheel’ sign, CEUS is superior to other modalities such as angiography, CTHA, and carbon dioxide-enhanced ultrasonography [18–20].

(3) When nodules previously diagnosed as DNs on CTHA, CT during arterial portography (CTAP), or biopsy should be monitored for malignant transformation:

By performing CEUS regularly, it is possible to monitor these nodules in the outpatient set-

tings to identify the appearance of intranodular arterial blood flow or a decline in the uptake of Sonazoid® in the Kupffer phase.

(4) When nodules are not hypervascular in the early arterial phase, but are hypovascular in the portal venous and equilibrium phases in contrast-enhanced CT:

A diagnosis of HCC can be made even in such nodules when arterial vascularity is observed on CEUS, since this technique is more sensitive in the detection of intranodular arterial blood flow than MDCT.

(5) When a navigation system for accurate needle insertion guidance is necessary for B-mode ill-defined HCC:

Defect reperfusion imaging can localize nodules in the Kupffer phase. After the re-injection of Sonazoid® to confirm the presence of arterial blood flow (defect reperfusion imaging), the Kupffer-phase image can be used to guide needle insertion for local ablation.

(6) When HCCs with typical hypervascularity in the arterial-phase CT have washout in the portal venous and equilibrium phases, which are ill-defined in B-mode US (including locally recurrent lesions):

The detection rate of viable HCC is 100% if defect reperfusion imaging is performed after detecting Kupffer-phase defects.

(7) When macroscopic morphologic diagnosis of nodules is needed before treatment:

Because the macroscopic morphology of HCC accurately reflects the malignancy grade of the tumor, morphological information is essential for the establishment of the correct treatment strategy. Among currently available imaging modalities, Sonazoid®-enhanced US most accurately displays the macroscopic morphology of HCC lesions [21, 22].

(8) To evaluate treatment response after RFA or TACE:

CEUS is the most sensitive evaluation method immediately after these procedures. Although fusion imaging is also used in RFA, it is possible to evaluate not only tumor response but also ablative margins by using CEUS [23, 24].

(9) For surveillance and staging of HCC:

In addition to a pilot study [13], a recent multicenter randomized prospective study showed that screening the entire liver by the Kupffer phase of Sonazoid®-enhanced US is a more sensitive method for the early detection of small HCCs compared with screening by B-mode US. It is therefore anticipated that entire liver screening in the Kupffer phase of Sonazoid®-enhanced US will be incorporated into clinical guidelines for the surveillance of HCCs based on this evidence. This imaging approach is also expected to play an important role in the staging of HCCs.

(10) For screening and staging of metastatic liver cancer and cholangiocarcinoma:

Whole-liver scanning in the Kupffer phase shows metastatic liver cancers as defects, thereby revealing a higher number of nodules than MDCT or B-mode US. Therefore, screening in the Kupffer phase of Sonazoid®-enhanced US should be incorporated into clinical practice to establish a treatment strategy for patients who have or are suspected to have 1–2 metastatic liver tumors.

Essentially, CEUS is recommended to increase the diagnostic accuracy of benign tumors (hemangioma, FNH, and DN) in outpatient clinics, and to aid in the screening and staging of metastatic liver cancer and HCC. Because of its high sensitivity in detecting intranodular arterial blood flow, CEUS is also useful for detecting small lesions that contrast-enhanced CT fails to identify.

As described earlier, US has conventionally been used as a screening tool. However, in recent years, CEUS has become an important tool for providing a thorough examination and a definitive diagnosis, demonstrating that it is indeed a breakthrough imaging technology.

## EOB-MRI

The commercialization of the hepatocyte-specific contrast agent Gd-EOB-DTPA began in 2008, placing it in a relatively new group of MRI contrast agents. This unique liver-specific contrast agent is taken up by hepatic parenchymal cells and is secreted into the bile. Unlike other liver-specific agent such as superparamagnetic iron oxide (SPIO), Gd-EOB-DTPA show the hepatic parenchyma as white 20 minutes post-injection in the hepatocyte-phase of a T1-weighted MRI, while nodules that lack hepatic parenchyma, such as HCC, appear as hypointense signals. For this reason, Gd-EOB-DTPA is occasionally called 'white liver' agent. Compared with SPIO, which turns the entire liver black (also known as 'black liver' agent) in T2-weighted images with poor spatial resolution, Gd-EOB-DTPA is a user-friendly diagnostic imaging modality even for hepatologists who are not specialized in the use of MRI. Therefore, Gd-EOB-MRI is also a breakthrough in diagnostic liver imaging.

After intravenous administration, approximately 50% of Gd-EOB-DTPA is taken up by hepatocytes and excreted into the bile, while the rest is excreted by the kidneys. The uptake of the contrast agent into hepatocytes is known to occur via passive diffusion mediated by organic anion transporter protein 1 (OATP1) in the cell membrane [25], while its excretion from hepatocytes into the bile canaliculi is thought to involve ATP-dependent active transport mediated by multidrug-resistance associated protein 2 (MRP2) [26].

Recent studies show that OATP1B3 (also referred to as OATP8) is responsible for the uptake of Gd-EOB-DTPA in humans [27, 28]. OATP1B3 is expressed in some of moderately- to well-differentiated hypervascular HCCs, and these neoplasms are visualized as hyperintense signals in the hepatocyte phase. However, no association exists between the expression of OATP1B3 and bile production or tumor differentiation [27]. These findings suggest that the expression of the uptake transporter OATP1B3 and the excretion-related transporter MRP2 are normal in DNs, causing no change in the uptake of the contrast agent in the hepatocyte phase. In well-differentiated early HCCs accompanied by stromal invasion, however, the expression of OATP1B3 is decreased, resulting in reduced uptake of the contrast agent, and thus generating hypointense signals in the hepatocyte phase. In well-differentiated as well as moderately- or poorly-differentiated HCCs, the expression of OATP1B3 is reduced or absent, presumably causing hypointense signals in the hepatocyte phase.

However, nodules in approximately 5–10% of hypervascular and moderately-differentiated HCCs are iso-to-hyperintense in the hepatocyte phase, and this type of nodule is known to have a favorable clinical outcome [28–30]. Even among hypervascular HCCs, nodules showing hyperintense signals in the hepatocyte phase have low alpha-fetoprotein and vitamin K antagonist-II levels and a low rate of intrahepatic metastasis, and thus a good prognosis. Based on these findings, it is possible to observe early HCCs in which OATP1B3 expression has not been downregulated during development from a DN to an early HCC and then to a well-to-moderately differentiated HCC. Indeed, in clinical practice, some nodules that are not hypointense in the EOB-MRI hepatocyte phase are subsequently diagnosed as well differentiated HCCs based on histological findings from the biopsy, suggesting that it is not unusual to find well-differentiated HCCs expressing OATP1B3.

Cases opposite to the above scenario, that is, DNs displaying hypointense signals in the hepatocyte phase, may be problematic. In clinical practice, some nodules showing hypointense signals in the hepatocyte phase are subsequently diagnosed as a DN following a biopsy. However, in a study examining resected specimens, but not biopsy samples, all DNs displayed isointensity in the hepatocyte phase [31]. According to expert opinion, in early HCC, it is extremely rare for DNs to be hypointense in the hepatocyte phase of EOB-MRI. Indeed, in our clinical experience, it is also extremely rare for hypointense resected specimens to be diagnosed as DNs [10]. Even when a diagnosis of a DN is made based on biopsy findings, there is

always a possibility of sampling variability. Furthermore, even liver specialized histopathologists have difficulty making a definitive diagnosis of early HCC [5] in the absence of stromal invasion in biopsied samples, despite their similar cellular or structural atypia. Further study is needed to address the diagnostic limitations of histopathological findings from biopsies.

Many early HCCs appear hypovascular in resected specimens, making their diagnosis difficult even by CTAP or CTHA. While many early HCCs show a slight decrease in portal venous blood flow, some are isodense on CTAP. In addition, many early HCCs that are hypointense on the hepatocyte phase of Gd-EOB-MRI are diagnosed as early HCCs upon histological examination [10]. Furthermore, most nodules that do not show decreased signals in the hepatocyte phase are identified as DNs in the resected specimens. Taking into account these findings, when differentiating early HCCs from DNs, the functional diagnostic ability of Gd-EOB-MRI, which sensitively captures early signs of carcinogenesis, is believed to be superior to hemodynamic or functional diagnosis of Kupffer cells such as the Kupffer phase of SPIO-MRI, Sonazoid®-enhanced US, or decreased portal venous flow on CTAP.

The following are unknown: (1) the frequency of DNs that display hypointense signals in the hepatocyte phase of EOB-MRI; (2) the frequency of hypovascular, hypointense nodules in the hepatocyte phase that are pathologically diagnosed as early HCC; (3) the frequency of future hypervascularization among these nodules; and (4) the factors associated with hypervascularization. These four questions should be addressed as soon as possible in multicenter studies with an adequate number of cases. Indeed, there are many reports of hypervascularization of hypovascular, hypointense nodules [32–50]. Tumor diameter and nodule growth speed are reported as risk factors for hypervascularization. These characteristics are therefore important in predicting the hypervascularization of hypovascular nodules. It should be noted that the tumor diameter cutoff in these studies has often been reported around 1 cm. Actually, intensive follow-up of hypovascular nodules that are hypointense in the hepatobiliary phase of EOB-MRI has shown that nodules with a higher rate of growth are more prone to develop into hypervascular nodules, which suggests that nodule growth speed might be included in the algorithm as well.

The next question concerns the proper clinical management of these nodules. To address this issue, a multicenter prospective study must be performed to investigate their rate of malignant transformation. This should be done by obtaining histopathological findings from hypovascular nodules that are identified as hypointense in the hepatocyte phase of Gd-EOB-MRI and by following the natural course of these nodules.

In conclusion, proactive examination using EOB-MRI is recommended in the following settings: (1) the differentiation of early HCC from DNs; (2) staging of HCCs prior to treatment; (3) alternate use of MDCT and Gd-EOB-MRI for screening of HCCs in high-risk patients who are recommended to undergo MDCT or MRI 1–2 times annually [51]; (4) early detection of recurrence by the alternate use of MDCT and Gd-EOB-MRI during follow-up after treatment of HCC; and (5) preoperative detection and evaluation of metastatic liver cancers.

As stated above, CEUS and Gd-EOB-MRI play tremendously important roles in screening, definitive diagnosis, malignant potential, diagnosis of pathological differentiation grade, assessment of treatment response, treatment guidance, and early detection of tumor recurrence.

In this issue of *Liver Cancer*, detailed reviews of these two breakthrough imaging modalities are presented by Piscaglia and Salvatore [52] and Lee [53], and I believe these two articles are of tremendous value for readers of this journal.



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